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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/901,910	07/11/2001	Haodong Li	PF126P2	7856

22195 7590 09/21/2004

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INTELLECTUAL PROPERTY DEPT.
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EXAMINER	
GIBBS, TERRA C	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 09/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/901,910	LI ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12/23/03, 4/4/04, and 7/6/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14 and 28-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14 and 28-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/23/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Sequence search alignment*.

DETAILED ACTION

This Office Action is a response to Applicants Amendment and Remarks filed on December 23, 2003, Applicants Remarks filed April 4, 2004, and Applicants Election filed July 6, 2004.

Claims 15-27 and 56 have been canceled. New claims 53-55 are acknowledged. Claims 1-14 and 28-55 are pending in the instant application. Claims 1 and 14 have been amended.

Claims 1-14 and 28-55 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

In the previous Office Action mailed June 30, 2004, the Examiner required an election under 35 U.S.C. §121. In particular the Examiner had required restriction between a group consisting of the invention of claims 1(a-d), directed to methods utilizing polynucleotides encoding SEQ ID NO:2, polynucleotides encoding SEQ ID NO:7, polynucleotides encoding the CTGF-2 polypeptide encoded by the cDNA contained in ATCC Deposit No. 75804, and polynucleotides encoding a CTGF-2 polypeptide fragment with angiogenic activity, respectively. In response to this restriction requirement, Applicants have amended the claims to remove methods utilizing polynucleotides encoding SEQ ID NO:7. This amendment is found responsive to the previous restriction requirement mailed June 30, 2004. It is noted that a polynucleotide encoding SEQ ID NO:2 and the CTGF-2 polypeptide encoded by the cDNA contained in ATCC Deposit No. 75804 are the same embodiment, as recited in the instant specification at page 8,

[0038], or as recited at page 6, [0033], are thus related, and will be examined together. It is further noted that a CTGF-2 polypeptide fragment with angiogenic activity is encompassed within the embodiments of a polynucleotide encoding SEQ ID NO:2, and the CTGF-2 polypeptide encoded by the CDNA contained in ATCC Deposit No.75804, are thus related, and will be examined together.

Information Disclosure Statement

Applicants Information Disclosure Statement, filed on December 23, 2003 is acknowledged. The references referred to therein have been considered on the merits.

Response to Amendment

Applicants Amendment filed April 19, 2004 to insert sequence identifiers into paragraphs [0021] and [0032] is acknowledged.

Priority

In the previous Office Action mailed July 29, 2003, the Examiner informed Applicant that the specifications of parent applications 08/459,101, now U.S. Patent 5,945,300 and PCT/US94/07736, now International Publication No. WO96/01896 were *not* enabling for a method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2, as the 08/459,101 and PCT/US94/07736 applications do not

provide any guidance or examples, prophetic or working, regarding the elected invention drawn to a method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2. It is further noted that in the previous Office Action mailed July 29, 2003, the Examiner informed Applicant that the presently claimed invention was given priority to U.S. Patent Application Serial No. 09/348,815, now U.S. Patent 6.534,630, filed July 8, 1999.

Response to Arguments

In response to this argument, Applicants argue that methods of administering the claimed polynucleotides are taught in the specification of the parent, USSN 08/459,101, now U.S. Patent 5,945,300. Applicants point the Examiner to page 21, third full paragraph. Applicants further argue that Example 3 of parent application 08/459,101, discloses a method by which a retroviral vector can be used to deliver the gene of interest to a mammalian host. Applicants contend that one in the art would be able to follow this protocol without undue experimentation to administer the polynucleotide encoding CTGF-2 to a mammal. Applicants also argue that support for stimulation of angiogenesis can be found at page 1, second paragraph, last sentence and page 3, first paragraph, last 2 lines, where would healing, tissue repair, and stabilization of tissue implants are discussed. Applicants contend that one of skill in the art would recognize that all these functions depend on stimulation of angiogenesis to occur. Applicants further argue that at page 3, sixth full paragraph, describes antagonists of CTGF polypeptides which would inhibit tumor growth. Applicants contend that one of skill in the art would recognize that a manner in which these antagonists function could be by inhibiting the angiogenesis stimulation by CTGF.

Applicant's arguments have been fully considered, but are not found persuasive. The Examiner has re-visited page 1, second paragraph, last sentence and page 3, first paragraph, last 2 lines, page 3, sixth full paragraph, and Example 3 of parent application 08/459,101. However, none of these disclosures support a method of **stimulating angiogenesis** in a mammal comprising the administration of a polynucleotide encoding CTGF-2. In fact, the term "stimulating angiogenesis" cannot be found in parent application 08/459,101. While parent application 08/459,101 discusses that generally CTGF is important in would healing, tissue repair, and stabilization of tissue implants, this statement is very vague and general and does not support a method of **stimulating angiogenesis** in a mammal comprising the administration of a polynucleotide encoding CTGF-2. Further, a description of antagonists of CTGF polypeptides which would inhibit tumor growth do not support a method of **stimulating angiogenesis** in a mammal comprising the administration of a *polynucleotide* encoding CTGF-2. While, Example 3, of 08/459,101 discloses a method by which a retroviral vector can be used to deliver the gene of interest to a mammalian host, this method does not contemplate, explicitly or inherently, a method of stimulating angiogenesis as instantly claimed.

It is noted that in the previous Office Action mailed July 29, 2003, the Examiner informed Applicant that the presently claimed invention is given priority to U.S. Patent Application Serial No. 09/348,815, now U.S. Patent 6,534,630, filed July 8, 1999. The Examiner has found this statement to be **incorrect** as U.S. Patent Application Serial No. 09/348,815, now U.S. Patent 6,534,630 does not have support for a method of **stimulating angiogenesis** in a mammal comprising the administration of a polynucleotide encoding CTGF-2. In fact, the term "stimulating angiogenesis" cannot be found in parent application 09/348,815. Although

Example 3 of 09/348,815 discloses a method by which a retroviral vector can be used to deliver the gene of interest to a mammalian host, this method does not contemplate, explicitly or inherently, a method of stimulating angiogenesis as instantly claimed. **Accordingly, all of the claims of the presently claimed invention have been given priority to U.S. Provisional Application Serial No. 60/217,402, filed July 11, 2000.**

Claim Rejections - 35 USC § 112

In the previous Office Action mailed July 29, 2003, claims 1-14 and 28-52 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This rejection is withdrawn** in view of Applicants amendment to the claims to remove the term "derivative".

In the previous Office Action mailed July 29, 2003, claims 1-14 and 28-52 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 29, 2003.

Response to Arguments

In response to this rejection, Applicants argue that the terms "an active fragment or derivative thereof" have been removed from the claims, therefore rendering the rejection moot with respect to these elements of the claims. Applicants further argue that the specification contains ample disclosure for the embodiments of the claims, as Applicants contend that species

within the scope of the claims have been contemplated and one of ordinary skill in the art would recognize members of the claimed genus. Applicants also argue that the test for the written description requirement is whether one of ordinary skill in the art could reasonably conclude that the inventor has possession of the claimed invention. Applicants rely on *Vas-Cath Inc. v. Mahurkar* and MPEP §2163.02.

Applicant's arguments have been fully considered, but are not found persuasive. The Examiner agrees that removing the term "an active fragment or derivative thereof" renders this rejection moot [with respect to these elements of the claims]. However, the broad claim, claim 1, is drawn to a method of stimulating angiogenesis in a mammal, comprising administering a **polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity** (see claim 1(d)). The specification discloses only SEQ ID NO:1 as a polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity. In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, SEQ ID NO:1 is the only sequence whose complete structure is disclosed. The specification does not provide any disclosure as to what would have been a polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity, other than SEQ ID NO:1. Further, the specification does not provide specific features and functional attributes that would distinguish different members of the claimed genus. Applicants' attention is directed to the decision in *In re Shokal*, 113 USPQ 283 (CCPA 1957) wherein is stated: It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. In re Soll, 25 C.C.P.A.

(Patents) 1309, 97 F.2d 623, 38 USPQ 189; In re Wahlforss et al., 28 C.C.P.A. (Patents) 867, 117 F.2d 270, 48 USPQ 397.

The instant specification does not teach a polynucleotide encoding a CTGF-2 polypeptide fragment, nor has the protein been characterized by domains of activity. The specification discloses only the full length CTGF-2, as represented in SEQ ID NO:1, as a polynucleotide encoding a CTGF-2 polypeptide with angiogenic activity. This limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus. Therefore, only SEQ ID NO:1, but not the full breadth of the claim, meets the written description provision of 35 USC 112, first paragraph.

It is noted that new claim 55 is also included in this rejection, as it recites, a method of stimulating angiogenesis in a mammal comprising administering a polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity.

In the previous Office Action mailed July 29, 2003, claims 1-14 and 28-52 were rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550, does not provide enablement for a method of stimulating angiogenesis in a mammal, comprising any route of administration of a polynucleotide encoding

CTGF-2, wherein the mammal has restenosis. **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 29, 2003.

Response to Arguments

In response to this rejection, Applicants argue that the specification at page 53, teaches the nucleic acids encoding CTGF-2 are administered to stimulate angiogenesis to mediate a therapeutic effect. Applicants contend that one of skill in the art would recognize that the therapeutic effect would be for any condition in which angiogenesis stimulation was necessary, including restensosis and not limited to ischemia. Applicants rely on references AI and AJ listed in the Information Disclosure Statement filed December 23, 2003. Applicants further argue that the specification teaches various routes of administering to use in making the invention and one of skill in the art would be able to readily use these teachings. Applicants also argue that the specification teaches a variety of vectors can be used to introduce the polynucleotides into cells and one of skill in the art would be able to readily use these teachings. Moreover, Applicants argue that the specification need only enable a person of ordinary skill in the art to make the claimed polynucleotides and practice a single use of the claimed polynucleotides without undue experimentation. Applicants rely on *In re Wands*. Applicants argue that Example 12 of the specification shows angiogenesis stimulation data from the *in vivo* delivery of CTGF-2 and this one example alone meets the requirement of enabling one of ordinary skill in the art a single use for the claimed polynucleotides without undue experimentation. Applicants argue that the Anderson reference (1998), used to support the position that human gene therapy is experimental

and unpredictable, also states that there are over 300 clinical protocols for gene therapy that have been approved. Applicants argue that the Anderson reference (2002), used to support the position that human gene therapy is experimental and unpredictable, also predicts success for gene therapy and is enthusiastic about the wide range and future success of gene therapy. Applicants argue that the Crystal reference, used to support the position that human gene therapy is experimental and unpredictable, also describes various studies that show successful gene transfer and numerous studies in which there was *in vivo* evidence of gene transfer. Applicants argue that the Branch reference, used to support the position that human gene therapy is experimental and unpredictable, is a review of antisense RNA technology, rather than gene therapy *per se* and the nature of antisense molecules is entirely different from gene therapy vectors. Applicants contend that theses references are enthusiastic about the success of gene therapy and are not germane to the patentability of the present invention.

Applicant's arguments have been fully considered, but are not found persuasive. Although the instant specification teaches various routes of administering the claimed polynucleotides of the invention and a variety of vectors can be used to introduce the polynucleotides of the invention, only the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550, was shown to be effective in stimulating angiogenesis. Given the discussions that human gene therapy is experimental and unpredictable, one skilled in the art would need to undergo undue experimentation to practice the full scope of the invention. This undue experimentation would include the sufficient systemic delivery of a polynucleotide encoding CTGF-2 to specific intracellular targets in quantities sufficient to stimulate angiogenesis in a mammal; the sustained and regulated expression of

expression vectors comprising a polynucleotide encoding CTGF-2 in organ systems and cells in a mammal in a quantity that was sufficient to stimulate angiogenesis.

As discussed in the previous Office Action mailed July 29, 2003, Anderson, WF (Nature, 1998 Vol. 392(6679 Suppl):25-30 teaches several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered. The reason for the low efficiency of gene transfer and expression in human patients is that we still lack a basic understanding of how vectors should be constructed, what regulatory sequences are appropriate for which cell types, how *in vivo* immune defenses can be overcome, and how to manufacture efficiently the vectors that we do make. It is not surprising that we have not yet had notable clinical success (see pages 25 and 30). As further discussed in the previous Office Action mailed July 29, 2003, a very recent review regarding the current status of clinical gene therapy, asserted that the reason that gene therapy has been so long in coming is because successful gene therapy in human patients is much more complex than obtaining success in treating mice (see Anderson, WF (Human Gene Therapy, 2002 Vol. 13:1261-1262) (see page 1261, first column, last paragraph)). Applicants argue that these reference are not germane to the to the patentability of the present invention, however, these reference clearly teach that at the time the invention was made, human gene therapy was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acid gene therapy *in vivo*. It is noted that Applicants have not provided any evidence, in the form of exhibits or appendices, to show that the current status of gene therapy is a routine and predictable art. Therefore, the references relied upon by the Examiner to support the position that human gene therapy is unpredictable are believed to represent a true state of the art.

Regarding Applicants arguments that Example 12 of the specification shows angiogenesis stimulation data from the *in vivo* delivery of CTGF-2, and this one example alone meets the requirement of enabling one of ordinary skill in the art a single use for the claimed polynucleotides without undue experimentation, the *Wands* factors have been considered in formulating this rejection and favor undue experimentation. For example, the specification provides methodologies for a method of stimulating angiogenesis at the site of ischemia in a mammal, comprising the intramuscular administration of SEQ ID NO: 1, wherein SEQ ID NO: 1 is contained in adenoviral vector pTG14550. The specification fails to teach the successful delivery of a polynucleotide encoding a CTGF-2 polypeptide fragment with angiogenic activity, other than SEQ ID NO:1, as contemplated in the instant claims (as per the 35 U.S.C. 112, first paragraph rejection above at page 6 for written description). Therefore, undue experimentation, particularly in the form of determining those polynucleotides, other than SEQ ID NO:1, which encode a CTGF-2 polypeptide fragment with angiogenic activity, which stimulate angiogenesis, would be required of a person of skill in the art to make and use the claimed invention, where no specific features and functional attributes of said polynucleotide have been provided. Further, the instant specification contemplates any route of administration and any adenoviral vector for delivery of the polynucleotides of the instant invention to stimulate angiogenesis, where the art teaches vector-based therapy is highly unpredictable due to general inefficiency at achieving successful gene transfer as well as a general lack of available data regarding repetitive administration of DNA to whole organisms. Therefore, in view of the *Wands* factors, undue experimentation would be required of the skilled artisan to practice the claimed invention.

It is noted that new claims 53-55 are also included in this rejection.

Claim Rejections - 35 USC § 102

In the previous Office Action mailed July 29, 2003, claims 1, 2, 7, 9, 13, 31, and 35 were rejected under 35 U.S.C. 102(b) as being anticipated by Babic et al. (Proc. Natl. Acad. Sci., 1998 Vol. 95:6355-6360). **This rejection is maintained** for the reasons of record set forth in the previous Office Action mailed July 29, 2003.

Response to Arguments

In response to this rejection, Applicants argue that the instant invention is entitled to priority of the parent application, 08/459,101, as well as PCT/US94/07736, filed July 12, 1994. Applicants also argue that assuming *arguendo* Babic et al. is properly considered as prior art, Babic et al. used purified CYR61 protein carried by Hydron pellets, and not full length mouse CYR61 cDNA in a pL61SN vector, as suggested by the Examiner. Applicants argue that the method of Babic et al. is not relevant to the claimed invention, since Babic uses purified proteins and the instant application contemplates the use of polynucleotides.

Applicant's arguments have been fully considered, but are not found persuasive. Applicants argue that the instant invention is entitled to priority of the parent applications, 08/459,101, as well as PCT/US94/07736, filed July 12, 1994. This is not found persuasive because as per the Examiners assessment of priority as discussed above, parent applications,

08/459,101 and PCT/US94/07736, do not have support for a method of stimulating angiogenesis in a mammal comprising the administration of a polynucleotide encoding CTGF-2, as the term "stimulating angiogenesis" cannot be found in either of the applications. Accordingly, the presently claimed invention has been given priority to U.S. Provisional Application Serial No. 60/217,402, filed July 11, 2000. Therefore, Babic et al. is considered as prior art.

Applicants also argue that the method of Babic et al. is not relevant to the claimed invention, since Babic uses purified proteins and the instant application contemplates the use of polynucleotides. This is not found persuasive because Babic et al. disclose the expression of the mouse CYR61 cDNA, under the regulation of a constitutive promoter in RF-1 gastric adenocarcinoma cells, significantly enhances the tumorigenicity of these cells, as measured by growth in immunodeficient mice, following s.c. injection in the mouse flanks, resulting in tumors that are larger and more vascularized than control cells (see Figure 4), and reads on claims 1(d), 2, 7, 9, 13, 31, and 35 . It is noted that mouse CYR61 protein exhibits 89% identity and 93% similarity to CTGF-2 of the instant invention as discussed in the instant application at page 7 [0036]. Babic et al. further disclose that an increased size of CYR61-expressing tumors is related to the angiogenic activity of CYR61 (see discussion at page 6359, first and second columns). Therefore, Babic et al. anticipate claims 1, 2, 7, 9, 13, 31, and 35.

It is noted that claim 55 is also included in this rejection.

The following is a new rejection:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 39-41, and 53-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Lau et al. [WO 97/33995].

Lau et al. disclose, for example, a method of screening for a modulator of angiogenesis comprising the steps of: (a) contacting a first biological sample capable of undergoing angiogenesis with a biologically effective (i.e. angiogenically effective) amount of an ECM signaling molecule-related biomaterial and a suspected modulator (inhibitor or potentiator); (b) separately contacting a second biological sample with a biologically effective amount of an ECM signaling molecule-related biomaterial, thereby providing a control; (c) measuring the level of angiogenesis resulting from step (a) and from step (b); and (d) comparing the levels of angiogenesis measured in step (c), whereby a modulator of angiogenesis is identified by its ability to alter the level of angiogenesis when compared to the control of step (b), wherein the ECM signaling molecule is human Cyr61 (see page 11, last paragraph). It is noted that the protein sequence of human Cyr61 disclosed by Lau et al. (see Lau et al. SEQ ID NO :4) is almost 100% identical to SEQ ID NO:2 of the instant invention (see attached sequence alignment). It is further noted that SEQ ID NO:3 of Lau et al. is the polynucleotide encoding SEQ ID NO:4. **It is further noted that step (b) of Lau et al. reads on claims 1 (a) and (d), 53-54.** Lau et al. further disclose, for example, a method of screening for a modulator of cell adhesion comprising the steps of: (a) preparing a surface compatible with cell adherence; (b) separately placing first

and second biological samples capable of undergoing cell adhesion on the surface; (c) contacting a first biological sample with a suspected modulator and a biologically effective amount of an ECM signaling molecule-related biomaterial selected from the group consisting of a human Cyr61, a human Cyhr61 fragment, a human Cyr61 analog, and a human Cyr61 derivative; (d) separately contacting a second biological sample with a biologically effective amount of an ECM signaling molecule-related biomaterial selected from the group consisting of human Cyr61, a human Cyhr61 fragment, a human Cyr61 analog, and a human Cyr61 derivative, thereby providing a control; (e) measuring the level of cell adhesion measured in step (e), whereby a modulator of cell adhesion is identified by its ability to alter the level of cell adhesion when compared to the control of step (d) (see page 13, last paragraph). **It is noted that step (d) of Lau et al. reads on claims 1(d) and 55.**

Lau et al. also disclose, for example, Cyr61, in the presence or absence of a suspected modulator, is surgically implanted into the corneas of mammalian laboratory animals and measurements of the development of blood vessels in the implanted corneas is assessed (see Example 19), and reads on claims 1, 53, and 54. Lau et al. claim, for example, a method of inducing wound healing in a tissue comprising contacting wounded tissue with an angiogenically effective amount of Cyr61 (see claim 49), and reads on claims 1, 39, 41, 53, and 54. Lau et al. also claim, for example, a method of inducing wound healing in a tissue comprising the steps of (a) introducing a nucleic acid comprising a control expression sequence operably linked to an ECM signaling molecule into the cells of a wounded tissue; and (b) controlling the expression of said coding region, thereby inducing wound healing, wherein the nucleic acid comprises a vector

selected from an adenovirus, and wherein the ECM signaling molecule is human Cyr61 (see claims 50-52), and reads on claims 1, 2, 39, 40, 53, and 54.

Therefore, Lau et al. anticipate claims 1, 2, 39-41, and 53-55.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
September 15, 2004

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Sequence search alignment...

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RESULT 10
AAW35730
ID   AAW35730 standard; protein; 381 AA.
XX
AC   AAW35730;
XX
DT   27-MAR-1998  (first entry)
XX
DE   Human cysteine rich protein 61 (Cyr61).
XX
KW   Cysteine rich protein 61; Cyr61; human;
KW   extracellular matrix signalling molecule; cell adhesion; cell migration;
KW   cell proliferation; angiogenesis; chondrogenesis; oncogenesis;
KW   haematostasis; wound healing; organ regeneration.
XX
OS   Homo sapiens.
XX
PN   WO9733995-A2.
XX
PD   18-SEP-1997.
XX
PF   14-MAR-1997;   97WO-US004193.
XX
PR   15-MAR-1996;   96US-0013958P.
XX
PA   (MUNI-) MUNIN CORP.
XX
PI   Lau LF;
XX
DR   WPI; 1997-470875/43.
DR   N-PSDB; AAT94699.
XX
PT   Isolated and purified cysteine rich protein 61, Cyr61 - useful to
PT   modulate e.g. haematostasis, induce wound healing, promote organ
PT   regeneration etc.
XX
PS   Claim 2; Page 112-113; 133pp; English.
XX
CC   This protein sequence comprises human cysteine rich protein 61 (Cyr61),
CC   an extracellular matrix signalling molecule. Its amino acid sequence was
CC   deduced from a human placental cDNA clone (see AAT94699). Cyr61
CC   polypeptides can be expressed in transformed or transfected host cells.
CC   Cyr61 can be used to modulate haematostasis, induce wound healing in a
CC   tissue, promote organ regeneration, improve tissue grafting or promote
CC   bone or prothesis implantation (claimed). It can also be used to screen
CC   for a modulator of angiogenesis, chondrogenesis, oncogenesis, cell
CC   adhesion, cell migration, cell proliferation, expand a population of
CC   undifferentiated haematopoietic stem cells in culture and to screen for a
CC   mitogen (claimed). Ex vivo methods for using mammalian extracellular
CC   matrix signalling molecules to prepare blood products are also provided
XX
SQ   Sequence 381 AA;

  Query Match             99.6%;  Score 2106;  DB 2;  Length 381;
  Best Local Similarity   99.5%;  Pred. No. 4.6e-152;
  Matches  379;  Conservative    1;  Mismatches    1;  Indels    0;  Gaps    0;

Qy          1 MSSRIARALALVVTLLHLTRLALSTCPAACHCPLEAPKCAPGVGLVRDGCGCCKVCAKQL 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSSRIARALALVVTLLHLTRLALSTCPAACHCPLEAPKCAPGVGLVRDGCGCCKVCAKQL 60

Qy         61 NEDCSKTQPCDHTKGLECNFGASSTALKGICRAQSEGRPCEYNSRIYQNGESFQPNCKHQ 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||:||
Db         61 NEDCSKTQPCDHTKGLECNFGASSTALKGICRAQSEGRPCEYNSRIYQNGESFQPNCQHQ 120

Qy        121 CTCIDGAVGCIPLCPQELSLPNLGCPNPRLVKVTGQCCEEWVCDEDSIKDPMEDQDGLLG 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 CTCIDGAVGCIPLCPQELSLPNLGCPNPRLVKVTGQCCEEWVCDEDSIKDPMEDQDGLLG 180
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181 KELGFDASEVELTRNNELIAVGKGSSLKRLPVFGMEPRILYNPLQGQKCIVQTTSWSQCS 240
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
181 KELGFDASEVELTRNNELIAVGKGRSLKRLPVFGMEPRILYNPLQGQKCIVQTTSWSQCS 240

241 KTCGTGISTRVTNDNPECRLVKETRICEVRPCGQPVYSSLKKGKKCSKTKKSPEPVRFTY 300
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
241 KTCGTGISTRVTNDNPECRLVKETRICEVRPCGQPVYSSLKKGKKCSKTKKSPEPVRFTY 300

301 AGCLSVKKYRPKYCGSCVDGRCCTPQLTRTVKMRFRCEDGETFSKNVMMIQSCKCNYNCP 360
    ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
301 AGCLSVKKYRPKYCGSCVDGRCCTPQLTRTVKMRFRCEDGETFSKNVMMIQSCKCNYNCP 360

361 HANEAAFPFYRLFNDIHKFRD 381
    |||||||||||||||||||||
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